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The Enemies Without and Within
Cancer and the History of the Laboratory Sciences

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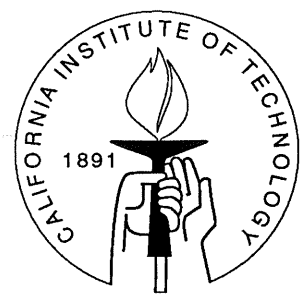

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It is well known that national defense has long been a stimulant to research and development and that in most of the industrialized countries since World War II, it has acted as a mighty engine of innovation, fostering -- and profiting from -- an immense range of programs for scientific research and training. In the name of deterring enemies, the American government has sponsored investigations in fields ranging from nuclear physics and microelectronics on the one side to mathematical logic and various branches of psychology on the other. I would like to suggest that in the twentieth century defense against disease has played a similar energizing role in the laboratory sciences and that no disease has been more aptly analogous to national defense in its uses and generation of scientific research than that most dread enemy of health -- cancer.

In the United States -- to which I will largely confine myself here -- the metaphor of battle has pervaded discourse on the drive to understand, ameliorate, and cure cancer since early in this century, not to mention in more recent years, when President Richard M. Nixon initiated a federal crash program -- the War on Cancer that began in 1971 -- to combat the disease. In the 1920s, cancer surpassed tuberculosis in the American mortality tables and became the second most prevalent cause of death, behind heart disease, where it remains today. Increasingly through these decades, cancer has loomed in public perception as the disease to be feared above all others if only because, like a terrorist, it tends to strike without reason or warning everywhere on the socioeconomic scale and because so many of its forms continue to defy cure.

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The century-long war has been carried out on many fronts -- in the clinic, the operating room, and the epidemiological field -- but also, with steadily mounting commitment and illumination, in the laboratory. This war may not yet have produced many therapeutic or curative victories, but it has been greatly affected by the experimental sciences and has had enormous effects upon them. Perhaps more than most modern stories of disease, it represents a rich interplay between, on the one side, human suffering, hope, and desperation and, on the other, the limits, exaggerated claims, and genuine prospects of scientific medicine. The development of cancer research is -- let us hope -- an unfinished story, yet I think that even now it offers itself as a useful organizing principle in the otherwise disparate field of the twentieth-century biomedical sciences.

Recognized since ancient times, the disease derives its name from the Greek for "crab," karkinos, expressing the tendency of cancers to claw in multiple directions into normal tissue. Similarly, the study of it -- oncology -- derives from the Greek oncos, for "mass." Nineteenth-century histologists, armed with the achromatic microscope, were able to recognize cancers in various organs as compositions of disorganized, abnormal cells. Rudolph Virchow, who wrote an entire book about cancer, encouraged the idea that most tumors were proliferations of cells from existing organs -- that they were by and large organ specific. For centuries, physicians knew no treatment for cancer other than surgical removal of accessible organs; perhaps the most widely practiced was mastectomy, which before the days of antisepsis involved searing off the breast with a red hot knife.

Galen, whose authority in the matter prevailed at least until 1500 A.D., attributed cancer to an excess of black bile, one of the four humors. Some of his successors at theorizing found the origins of cancer in -- variously -- immoral behavior, venery, depression, or (in the case of nuns) celibacy. Others, noting the tendency of some cancers to cluster in families, located the source in heredity. Here and there, from the late eighteenth century onward, several observers located the source in environmental poisons -- the soot in which chimney sweepers worked, the snuff and tobacco that gentlemen inhaled, the dust in mines, and the chemicals in aniline dyes. But at the end of the nineteenth century an honest reporter might have echoed what the leading Philadelphia surgeon Samuel Gross had written in the middle of it: "All we know, with any degree of certainty, [about cancer] is that we know nothing."

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However, from the late nineteenth century onward, the increasing spread of laboratory methods into the life sciences became not only a surgical but an experimental science -- and a well-supported one, too. Let me examine these developments by exploring, first, the period between the 1880s and the outbreak of World War II, and, then, the period since the Second World War.

Even in the first period, endowments, hospitals, and institutes were established for clinical and experimental investigations into cancer. Subventions came from state legislatures and the rich, often benefactors who had lost loved ones to cancer and who settled individual sums -- for example, $1.5 million to Columbia University in 1910 and $10 million to Yale in 1936 -- on institutions for cancer research that physical scientists of the day could only dream about. To this period can be traced the origins of many of the major cancer research facilities in Europe as well as in the United States. Towards the end of this period, the crusade against cancer enlisted the federal government, with the creation, in 1937, of the National Cancer Institute (NCI), which was given enough money in its first year of operation virtually to double national expenditures on the disease.

It is likely that the greater proportion of these resources was devoted to clinical rather than basic biological research, and a degree of faddishness marked the uptake by cancer researchers of new trends in the life sciences. Thus, in the late nineteenth and early twentieth centuries, the advent of infectious theories of disease stimulated a search in many laboratories for cancer-causing microorganisms, including protozoa, bacteria, spirochetes, and molds. This program failed and infectious theories of cancer were waning in scientific respectability when, in 1911, at the Rockefeller Institute for Medical Research, the young biologist Peyton Rous demonstrated that a tumor could be induced in a healthy chicken with a non-filterable agent -- a virus -- obtained from a malignancy in a cancerous one. However, although Rous' discovery revived the infectious theory for a time, scientists of his day were unable to observe similar viral transmission of cancers in other animals, and so the theory fell into deep disrepute in most -- though not all -- circles of oncology.

Cancer studies mirrored almost every new development in the experimental life sciences. In 1902, the German biologist Theodor Boveri attributed cancer to abnormal chromosomes, drawing upon his own embryological observations of chromosomal oddities in sea urchins, which he extended to the study of mitoses in tumors. In the early 1920s, the biochemist Otto Warburg, in the course of his work on cellular metabolism, discovered that cancer cells underwent anaerobic glycolysis, and he proposed that a possible cause of

cancer was cellular anoxia. Other scientists attempted to marshall the new Mendelian genetics to obtain a purchase on the tendency of cancer to run in families. And in the 1930s, developments in endocrinology stimulated not only theories but some laboratory demonstrations that sex hormones could induce mammary tumors in mice.

The steady integration of chemistry and biology prompted searches for carcinogenic materials and for analyses of their carcinogenic specificity -- that is, chemical determinations of what it is in, for example, soot, that causes cancer. The specifications were assisted by the arsenal of tools that chemistry was acquiring from physics. In 1932, the use of fluorescent spectra enabled the identification of the organic compound in coal tar that is carcinogenic, an accomplishment that fostered numerous attempts -- most of them fruitless apparently -- to account for oncogenesis in terms of the chemical structure of carcinogens. In 1938, W.C. Hueper, a German immigrant chemist employed at DuPont and concerned with bladder cancer among aniline dye workers, was able to demonstrate that repeated subcutaneous injections of 2-napthylamines induced bladder cancer in dogs. According to Hueper, DuPont not only refused to permit him to publish his results but also fired him.

By and large before World War II, each of the oncological indications from the experimental life sciences apparently failed to lead anywhere fast -- because it was ambiguous and uncertain; or because, like Rous's viral hypothesis, it sputtered as a research program; or because, like Hueper's observations, it threatened powerful economic interests. Many of these indications were celebrated in the press -- no doubt with the cooperation of scientists -- with the consequence that hopes were raised only to be dashed. It is understandable that a certain skepticism seems to have set in concerning the merits of the latest theory of cancer and promises for cures.

Yet certain parts of the work, comprising something more than evanescent embrace of scientific fashion, left scientifically lasting legacies. Some of these legacies were in the materials and methods devised in the attempt to transform oncology itself into an experimental science. Thus, early in the century, tumors were transplanted into mice, establishing rodents as agents of controllable and reproducible oncogenic experiment. During the 1920s, particular mouse lines were bred to be highly susceptible to tumors, leading to sublines that are ubiquitous in the current world of research, and the Roscoe B. Jackson Memorial Laboratory in Bar Harbor, Maine -- today the leading supplier of standardized mouse strains in the United States -- was founded in part to develop and

maintain lines of inbred mice for the purpose of establishing the genetics of cancer on a sound experimental basis.

The drive to extend experimental cancer research also contributed to the invention of tissue-culture techniques that would become fundamental in many fields of experimental biology and that also permitted the study in vitro of the conversion of normal cells into cancerous ones. One of these cultures came to be known as HeLa -- because it was derived from an aggressive cancer of the cervix of a woman named Henrietta Lacks (or possibly Helen Lane or Helen Larson) -- and the line would come to perform myriad services through the world of experimental biology, outliving both the eponymous patient and her cytologist.

Faddishness in the embrace of new developments in the laboratory sciences was particularly marked on the therapeutic side of cancer. Clinicians -- both caring and ambitious in varying proportions -- and desperate patients together formed a community of demand for cures. After Paul Ehrlich found his magic bullet of salvarsan, in 1906, he tried to find a magic bullet for cancer, too. Drug companies exploited brute-force experimental protocols to discover chemotherapeutic agents, injecting cancerous mice with a variety of compounds, some of which they advertised as products with "striking therapeutic effects." However, the most promising therapeutic dividends from the experimental sciences appeared to come from the new marvels that emerged from turn-of-the-century experimental physics -- radioactivity and X rays.

Pierre Curie himself helped pioneer what came to be called "Curietherapy" -- the use of radium to destroy tumors. Early clinical successes led to the establishment in 1909 of the Radium Institute affiliated with the Institut Pasteur, where scientists and physicians might conduct studies on the physics, biology, and clinical uses of the element. The Radium Institute commanded ample monies, Madame Curie as the director of its physics branch, and the able physician Claudius Regaud as head of its biomedical counterpart across the garden. Radiophysics, radiobiology, and radiomedicine all flourished at the Institute, and millions of additional francs came to it -- some of them from the women of America, who raised $100,000 to buy Madame Curie a gram of radium on the occasion of her visit to the United States in 1921. She was toasted from Yale to the White House, where President Harding gave her the radium itself, before some six hundred senators and congressmen, diplomats and scientists, wives and leading women.

X-ray therapy for cancer was tried within a few years after their discovery, in 1895, but initial successes in burning out malignancies were soon overshadowed by the

tendency of the crude early technology to combine with ignorance of the dose response in living tissue to burn out the patient or, as was clear by 1914, iatrogenically to cause cancer. However, although enthusiasm for X-ray therapy declined as that for Curietherapy mounted, it began to revive around 1930 when more was known about the impact of high-energy radiation on living tissue and X-ray technologies were under development that promised to be more precisely controllable, targetable, and penetrating.

That expectation brought cancer philanthropy within the reach of physicists who were developing more powerful tubes with which to accelerate atomic particles to explore the nucleus. Such support assisted the Caltech physicist C. C. Lauritsen in building a high-power X-ray tube that might speed particles to one million volts of energy, and the Berkeley physicist David Sloan, one of Ernest O. Lawrence's proteges, to develop an X-ray tube that supplied a beam as intense and energetic as half the world's purified radium.

By then the biggest assault weapon against the nucleus was the cyclotron. Lawrence, bolstered by his brother John, a physician who came to guide radiobiological work in the laboratory, touted neutrons and radioisotopes, which cyclotrons could produce in abundance, as potentially more effective than X rays in treating human cancer. Like the Radium Institute in Paris, the Radiation Laboratory at Berkeley embarked on radiobiological research -- though with less rigor -- first with mice and then, in 1938, with people, including one Robert Penney who was the first patient to be zapped with neutrons from the 60-inch accelerator. Private cancer money helped significantly to build the 60-inch, and in the late 1930s Lawrence's laboratory received tens of thousands of dollars from the new National Cancer Institute. Lawrence himself sat with the Nobel Laureate physicist Arthur Holly Compton as a committee of two to decide how to spend up to $100,000 a year of NCI money on the improvement of cyclotrons operating in the United States. As John Heilbron and Robert Seidel have told us in their study of Lawrence and his laboratory, all but two of the cyclotrons commissioned in the United States after 1936 were dedicated largely to biomedical work, meaning mainly cancer research. Yet virtually every physicist welcomed these machines primarily for the same reason that Ernest Lawrence had, privately, praised David Sloan's X-ray tube -- that is, for its "terrific effectiveness" in producing intense beams of high-energy protons for bombarding nuclei.

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After World War II, it was widely proclaimed that America's foreign foes had been defeated in the laboratories and that in the peace science, sufficiently mobilized, could defeat her people's domestic enemies, including cancer. Stafford Warren, the medical research director of the Manhattan Project and a specialist in radiation, told Congress in 1946 that dealing with "the cancer problem is no more impossible than the atomic bomb."

Wartime technical developments paid dividends in peacetime therapies. Microwave technology contributed to the building of sleek, compact linear accelerators for radiotherapy. Nuclear reactors produced artificially radioactive elements in quantities far more abundant than those that cyclotrons could spew forth, and in 1949, the recently created Atomic Energy Commission announced that it was giving away $500,000 worth of radioactive chemicals for use in the war against cancer. Reader's Digest, pointing out that radioactive cobalt could be surgically implanted, extolled the element as "the poor man's radium" and the "greatest, most beneficial dividend from the A-bomb." Wartime research had also revealed that nitrogen mustards could destroy human lymphomas. That discovery led promptly to the development of the first generation of effective chemotherapeutics, including the folic acid antagonists that Sidney Farber used in 1947 to achieve temporary remissions of acute leukemia in children.

Amid the postwar propensity to enlarge federal investment in research, such successes helped stimulate enormous increases in the budget of the National Cancer Institute, which climbed from $18 million at the beginning of the Eisenhower years to $110 million by the end of them. Equally a stimulus was the American Cancer Society, which, beginning with its takeover by Mary Lasker and her friends in the mid-1940s, became an aggressive lobby for cancer appropriations and also a ferocious fund-raising force on its own. As in many other areas of the biomedical sciences, private philanthropy and fund-raising campaigns continued to play a significant role in providing resources for clinical and biological research into the disease. The American Cancer Society, which raised ever-more millions each year, soon began to spend a quarter of its budget on grants for research, and acknowledgments for its subventions can be found in many important biomedical research papers. Public and private support conjoined in many places to transform research hospitals and facilities into institutions that now tower on the biomedical landscape -- for example, the Fox Chase Cancer Research Center, in Philadelphia; the Roswell Park Memorial Institute, in Buffalo, New York; the M.D. Anderson Hospital for Cancer Research at the University of Texas; and the Memorial-Sloan-Kettering Hospital, in New York City.

The war -- and the Cold War -- heightened awareness of environmental causes of cancer, starting with the fallout generated by atmospheric testing of nuclear weapons and spreading to other types of environmental toxics. In 1948, the National Cancer Institute hired William Hueper as head of its new Environmental Cancer Section. Under Hueper's laboratory program, the NCI identified an increasing number of chemical compounds as carcinogenic for animals -- and, by extensions, for human beings. Hueper's publications strongly influenced Rachel Carson in writing Silent Spring, which no doubt did more than any other book to popularize what epidemiologists and laboratory scientists had together learned about carcinogenesis. What they had learned was that cancer is often the product of enemies without, of oncogenic emanations and materials -- some of them, like ultraviolet radiation, in the natural environment but an increasing number of them in the human-made one. Silent Spring accelerated epidemiological and laboratory inquiries that would expose the carcinogenic qualities of an expanding range of chemical compounds -- for example, DES, the hormonal supplement for women -- and confirm the powerful likelihood, manifestly evident in the early 1960s, that smoking could cause cancer.

It seems that only a small fraction of the enormous resources that became available for cancer research in the quarter century after World War II were devoted to epidemiological studies of the disease. A considerable fraction of federal cancer research funds was given over to a cut-and-try search for chemotherapeutic compounds. The policy may well have pleased many industries; it displeased many scientists because in the then-current state of knowledge, the search was a hit-or-miss proposition, sufficiently Edisonian in character to provoke some critics to characterize the program as: "nothing to stupid to test."

Still, much of the national cancer research program was absorbed with investigations into the internal biological processes that led to malignancies. To most of the program's leadership, what was necessary to untangle this defiant puzzle were studies into fields of biology that seemed plausibly relevant to cellular metabolism, growth, regulation, and multiplication. Thus, the national cancer program was a major patron of basic research in molecular genetics, endocrinology, immunology, and biochemistry, including the laboratory methods, materials, and instrumentations essential for work in those areas.

By the early 1970s, it was also paying salient attention to the field pioneered by Peyton Rous -- tumor virology -- which field I will dwell on for the rest of this lecture

because its development sharply illustrates a number of the themes that I've been exploring and has proved to be dramatically important.

How tumor virology recovered from the disrepute into which it had fallen by World War I is a remarkable and extensive story in and of itself. Suffice it to say here that, despite the general rejection of Rous' claim that a virus might induce cancer, the idea had remained alive in research programs here and there -- notably at the Rockefeller Institute for Medical Research and at the Jackson Laboratories, in Bar Harbor -- which had slowly accumulated more evidence of viral oncogenesis in animals such as rabbits and mice. Operating far outside the main stream of biomedical research was the one-man program of an immigrant physician named Ludwik Gross. In 1950, while a staff member at a veteran's hospital laboratory in New York, Gross showed that he could induce leukemia with viruses in a particular inbred strain of newborn mice. Gross' work -- ignored until after it was confirmed five years later by an established biomedical researcher -- led in the later 1950s to the discovery of a number of animal tumor viruses and to an increasingly broad-based revival of the theory of viral oncogenesis.

And not only of theory but, in the 1950s and 1960s, to enormously productive laboratory studies in the subject. The progress profited significantly from the introduction of the techniques of phage genetics -- the quantitative analyses of plaques on uniform single layers of cells in culture -- into animal virology and their exploitation by Renato Dulbecco, working with the polyoma virus, to transform cells in vitro, that is, to provoke them to divide without restraint. At Caltech, Howard Temin and Harry Rubin, two proteges of Dulbecco, achieved the transformation of cells using similar techniques with what was coming to be called the Rous sarcoma virus. The phenomenon of transformation could be observed and quantified because it signaled its presence by the appearance of so-called foci on the flat face of the cell culture.

Beginning with the late Fifties, animal tumor virology of course benefitted also from the new knowledge that viruses consist of a protein coat wrapped around a core of nucleic acid -- either deoxyribonucleic acid (DNA) or ribonucleic acid (RNA). Dulbecco argued that cells are transformed when viral DNA is integrated into native cellular DNA, a contention that he proved experimentally in the 1960s. Or proved it at least for viruses like polyoma, which have DNA at their core. The issue of cellular transformation appeared to be rather more complicated in the case of the Rous sarcoma virus, whose core comprises RNA. DNA could code for RNA, but, as many of you know, the reverse was held to be

impossible -- which implied that RNA could neither integrate into cellular DNA nor could it generate any DNA to be integrated either.

However, Howard Temin insisted that viral RNA could generate double-stranded DNA complementary to it and thus act, as he wrote in 1964, "as a carcinogenic agent by adding some new genetic information to the cell." Temin, although ridiculed as scientifically wrongheaded, tenaciously accumulated experimental evidence in favor of his hypothesis as a young faculty member working in the McCardle Institute for Cancer Research, at the University of Wisconsin. Cancer research repaid the experimental life sciences when, in 1970, Temin decisively proved his hypothesis by reporting -- simultaneously with David Baltimore, another protege of Dulbecco's, then at MIT -- the discovery of the enzyme, soon dubbed reverse transcriptase, that catalyzed the synthesis of DNA from RNA.

By now research on animal tumor viruses had come to form a major branch of basic medical and biological science, spotlighting the achievement of Peyton Rous, who, in 1966, at age eighty-five, shared the Nobel prize in physiology or medicine for the work he had done 55 years earlier. After the dramatic achievements of Dulbecco, Temin, and Baltimore, it was tempting to leap from the demonstration that viruses were responsible for animal tumors to the belief that they must be the cause of human malignancies, too. A number of influential scientists enthusiastically took the leap -- for example, the chief of the laboratory of infectious diseases at the National Institutes of Health, who declared: "There isn't the slightest doubt in our minds that human cancers are caused by viruses."

It was that type of super scientific confidence that meshed with the political calculations of President Nixon to inaugurate the War on Cancer, which drove federal expenditure in the war against the "Big C," as John Wayne called it, to about one billion dollars a year by 1980. Yet the confidence was by no means universal among scientists, partly because the role of viruses in human -- as distinct from animal -- cancers was very unclear and partly because the basic mechanisms of cellular transformation were unknown. James D. Watson spoke for many scientific dissenters when he exclaimed that the proponents of the War had sold the American public a "nasty bill of goods about cancer," adding, with greater pungency than most of his colleagues might have publicly employed, that the whole enterprise was, as he put it, "a bunch of shit."

Although the full scientific impact of the War on Cancer awaits its historian, the main outlines of its consequences seem clear enough. Endless patrols were organized to search for viral agents of natural cancers. Few were flushed out for animal cancers and

none was found for the human variety. Neither did the war produce any dramatic new cures for cancer, a failure that drew denunciations of the campaign as a "medical Vietnam." However, the War on Cancer was not without its successes because it supplied the means to many investigators to pursue basic laboratory research in animal virology that they might have otherwise been unable to do -- and at least one of those projects led to profoundly striking and unexpected results.

The project was guided by two young biomedical scientists at the University of California, San Francisco, Medical School named Michael Bishop and Harold Varmus. In the early 1970s, they set out to test a hypothesis, recently advanced, that the cells of many, if not all vertebrates, must naturally contain carcinogenic stretches of DNA, stretches that had been named "oncogenes." The argument ran that oncogenes have the power to transform normal cells into tumor cells but that they are normally repressed -- meaning that they lie latent until they are activated by either natural or environmental causes. Bishop and Varmus focused specifically on a fragment of Rous sarcoma RNA that had recently been identified as the fragment in the virus that, when operated on by reverse transcriptase, became the DNA that turned normal chicken cells into sarcoma cells. Scientists referred to this viral DNA as the "sarc" oncogene. For Bishop and Varmus, the question was whether the viral sarc oncogene had a homologous counterpart in normal chicken-cell DNA.

By 1976, they had obtained results that surprised and exhilarated them: Homologues of the sarc gene appeared to be contained in the DNA not only of chickens but also of quail, turkeys, ducks, and even emus, one of the most primitive birds. No question about it: variations of sarc DNA did reside in the cellular DNA of many avian species. In 1978, Bishop and Varmus reported that they had also found closely related versions of the gene in the DNA of calves, mice, and salmon. They even had detected evidence of it in human DNA. Close relatives of the sarc gene -- that seed of cancer -- seemed to be everywhere.

Its virtual ubiquity led Bishop and Varmus to think about it in evolutionary terms. According to the fossil record, the major groups of species -- birds, mammals, and fish -- that embodied the gene had separated at least 400 million years earlier. To Bishop and Varmus, the plain evidence that the basic sarc gene had been conserved through so much time and speciation indicated that it might be involved in some critical cellular function -- the generation of structure, perhaps, or gene regulation. Indeed, tests showed that it was

active in normal cells, undergoing transcription into messenger RNA and translation into a protein.

Bishop and Varmus' results rapidly made oncogenes a major branch of basic biomedical research. The work was powerfully equipped by an arsenal of new experimental tools -- for example, recombinant DNA, gene sequencing, Southern blotting -- that had become available in molecular biology during the 1970s and that together permitted the rapid isolation, identification, and experimental manipulation of single genes. By the early 1980s, it was evident that a variety of oncogenes are to be found in different types of animal cancer cells, that many of these oncogenes are non-viral or the same as those found in viruses, and that -- most important -- many animal oncogenes are also human oncogenes

It was also evident that the oncogenes now demonstrated to reside in the normal cell are not quite the oncogenes -- the repressed tumor-causing DNA -- advanced in the original oncogene hypothesis. They are normal cellular genes. Most such genes seem to exist all over the tree of animal evolution, reinforcing Bishop and Varmus' idea that they must be involved in fundamental cellular processes, probably growth and differentiation. Almost all of them seem to express themselves -- that is, generate proteins -- during normal cellular development. Since they perform normal functions, cellular oncogenes are thus, strictly speaking, not oncogenes. They thus came to be termed "proto-oncogenes." They were recognized as normal genes that can somehow be turned into the agents of cancer -- friends of the body that can turn into foes. As such, Michael Bishop said, they are a kind of "enemy within."

H. G. Wells had declared in 1927: "The disease of cancer will be banished from life by calm, unhurrying, persistent men and women, working with every shiver of feeling controlled and suppressed, in hospitals and laboratories, and the motive that will conquer cancer will not be pity nor horror; it will be curiosity to know how and why." Wells' declaration is true in a number of respects; neither Dulbecco, Bishop, nor Varmus set out to discover the secret of cancer. However, others, like Temin, have been quite oncologically oriented. And it must be remembered that the martial metaphor has contributed enormously to establishing the opportunities of biomedical scientists, whatever their orientation, to satisfy their curiosity.

Like the scientific promises invoked for national defense, the claims made for cancer research over the decades have often been marked by exaggerated optimism, self-interested salesmanship, and grossly overstated estimates of the degree of threat from the

enemy. Clinical as well as laboratory oncology have both exploited the specter, and so has the environmental branch of the field -- for example, in the 1970s promulgating vastly overblown -- because they were vastly simplistic -- estimates of cancer deaths that would arise from carcinogens in the workplace and elsewhere in the environment. It is probably the case that in American democratic culture at least, it is impossible to mobilize resources for sustained explorations into the fundamental processes of nature and disease without the exaggerations of politics and public-relations promises of miracles around the corner. It is also the case that such campaigns, when guided by competent scientific authority, have yielded considerable scientific and technological dividends.

Indeed, like national defense, not only the war against cancer with a capital W but the long lower-case war against cancer has, especially in recent years, led through the experimental laboratory to remarkable scientific achievements. The theory of oncogenes that has come to prevail has opened the door to a biological union among the various stimuli to cancer -- radiations, chemicals, hormones, viruses, genes -- that the laboratory and epidemiological sciences have exposed since the turn of the century. All, it seems, were simply parts of the same elephant. The theory reveals that the enemies without are allied with enemies within. Indeed, their alliance has been demonstrated empirically -- by laboratory experiments that environmental carcinogens will turn normal cellular DNA into abnormal, oncogenic DNA.

Equally important, the advent of oncogenes has opened a new era in normal cellular biology. Since oncogenes are normal genes gone wrong, then identifying oncogenes is a powerful method of picking out and then analyzing the cellular role of genes that are involved in normal growth, regulation, and differentiation. Here again cancer research has repaid what it has borrowed from the laboratory sciences -- and repaid the debt handsomely. As Michael Bishop wrote in the spring of 1983, by studying the behavior of these genes, "we seek to solve not only the riddle of the cancer cell, but also the riddles of normal growth and development," adding, "The human intellect has finally laid hold of cancer with a grip that may eventually extract the deadly secrets of the disease."